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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,354	11/25/2003	Patrick L. Iversen	50450-8311.US03	8250
22918	7590	02/08/2006	EXAMINER	
PERKINS COIE LLP P.O. BOX 2168 MENLO PARK, CA 94026			EPPS FORD, JANET L	
			ART UNIT	PAPER NUMBER
			1633	
DATE MAILED: 02/08/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/723,354

Applicant(s)

IVERSEN, PATRICK L.

Examiner

Janet L. Epps-Ford

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 13-15 and 25-30 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 13-15 and 25-30 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION
Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9, 13-15, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims read on a method of inhibiting metabolism of a drug administered to a subject comprising co-administering with said drug a morpholino antisense oligomer effective to reduce expression of a cytochrome p450 enzyme that catalyzes metabolism of the drug in said subject. The claims read on the metabolism of any drug comprising administering antisense oligonucleotides targeting the broad genus of cytochrome p450 enzymes which encompasses enzymes selected from CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, CYP3A4, CYP6A1, cytochrome P450 enzymes from other organisms, and all other allelic and polymorphic variants of cytochrome P450 enzymes.

Additionally, the instant claims are drawn to a method comprising wherein a subject is administered a xenobiotic agent which induces the cytochrome p450 enzyme, wherein said enzyme includes all allelic and polymorphic forms, as well as all forms

isolated from all organisms in which it is expressed.

In the instant case, other than the antisense oligonucleotides according to SEQ ID NO: 16-35, and 46-47, Applicants have not shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. No guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed properties, since it is unknown what properties, structural or otherwise, that the antisense oligonucleotides of the present invention must possess for it to reduce the synthesis of a drug metabolizing cytochrome P450 enzyme that reduces the effectiveness of a drug.

Moreover, Applicants were not in possession of the full scope of molecules encompassed by the instant claims at the time of filing of the instant application, since it is apparent that further experimentation is required in order to determine the targeting sequences for the full scope of cytochrome p450 enzymes encompassed by the instant claims. Furthermore, additional experimentation would be required to identify the full scope of xenobiotic agents which induce the expression of the full scope of cytochrome P450 enzymes encompassed by the instant claims.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written

description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Absent the need for further experimentation, no guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed properties, since it is unknown what properties, structural or otherwise, that the antisense oligonucleotides of the present invention must possess for it to reduce the synthesis of a drug metabolizing cytochrome P450 enzyme that reduces the effectiveness of a drug. Additionally, although the instant claims are directed to a method, it is noted that the claimed methods require the use of a broad genus of compounds that are not sufficiently described in the specification as filed.

3. Claims 1-9, 13-15, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cytochrome

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P450 antisense comprising the administration of the antisense oligomers according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47, or compositions comprising said antisense oligomers, does not reasonably provide enablement for practicing the claimed invention comprising the use of antisense oligonucleotides targeting any cytochrome P450, other than the ones exemplified either *in vivo* (whole animal) or *in vitro*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Although, the specification does demonstrate the efficacy of the antisense oligonucleotides according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47 in the working examples, no guidance or working examples are disclosed that would allow a skilled artisan to use any other antisense oligonucleotides to inhibit cytochrome P450 *in vitro* or *in vivo*, nor does the specification as filed teach that the above antisense oligonucleotides can be used to inhibit the metabolism of all drugs. It is well known in the art that identification of target sites in a given mRNA at which antisense oligos bind to cause inhibition of translation is an unpredictable art. The skilled artisan would recognize that careful screening of oligonucleotides targeted to different sites on a given mRNA to find oligonucleotide binding sites for inhibition of translation, may fail to identify sites in the 5' untranslated region, the coding region, or in the 3'-untranslated region of the mRNA. The Applicants showing that several antisense oligos were ineffective in inhibiting cytochrome P450 expression, for example oligos according to SEQ ID NO: 16-17, 21-22 and 37-38 exemplify this point.

There is a significant amount of unpredictability associated with the clinical application of antisense oligonucleotide therapeutics. Crooke (1999), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate." (page 5, lines 12-16) Furthermore, Crooke describes a variety of factors that influences the activity and behavior of antisense-based compounds. These factors include oligonucleotide purity, oligonucleotide structure, target RNA structure and RNA protein interactions, variations in cellular uptake and distribution, and binding to and effects of binding to non-nucleic acid targets (pages 3-5). Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, the sequence of the oligonucleotide, and cell type. The effects of binding to non-nucleic acid targets may induce non-antisense effects that can be mistakenly interpreted as antisense or complicate the identification of an antisense mechanism. Additionally, such binding may also inhibit antisense activity of some oligonucleotides (page 5, 3rd paragraph). In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins, will be influenced by the chemical class of oligonucleotide studied (page 5, 4th paragraph). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical

developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target—often through an entirely unexpected mechanism.” In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Antisense therapy is a highly unpredictable and field and the skill in the art is high.

According to Stein (2000) “[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by nonsequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the methodology, attention must now also be paid to co-suppression of gene activity due to irrelevant cleavage.” Stein further states that “[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) eventually [*emphasis added*] may be possible.” (page 235, Concluding remarks) Stein clearly suggests that use of antisense oligonucleotide therapeutics are highly unpredictable due to “irrelevant cleavage” as a result of the low stringency requirements for RNase H activity, wherein a 5-base complementary region of oligomer to target may be sufficient to elicit RNase H activity (see Stein, abstract).

Crooke, Branch and Stein teach that the behavior of antisense based pharmaceuticals are unpredictable, therefore claims to antisense based

pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Additionally, Applicant's specification does not provide any evidence that the cytochrome p450 enzymes according to CYP1AA1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, CYP3A4, and CYP6A1, recited in the instant claims are responsible for the metabolism of every known conceivable drug in general. Applicants have not recited, for example, the CYP3A5 P450 enzyme, the alcohol dehydrogenases, the acetaldehyde dehydrogenases, or the dihydropyrimidine dehydrogenase (see Ingelman-Sundberg, 2001, page 194, paragraph 2). The instant claims broadly encompass the inhibition of the metabolism of any drug by means of co-administration of a morpholino antisense oligomer targeting the cytochrome p450 enzymes listed above.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary therapeutic effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In view of the breadth of the claimed invention, specifically in regards to the method of inhibition of the metabolism of any generic drug, the lack of description in

regards to the sequence of the broad genus of morpholino oligomers used in the claimed method, the lack of sufficient guidance in regards to the use of morpholino oligomers *in vivo*, the unpredictability associated with the behavior of an oligomer within a cell as it relates to the sequence composition of the oligomer, it is concluded that undue experimentation would be required to practice the full scope of the claimed invention, in particular using oligomers to inhibit the metabolism of drugs that are metabolized by the P450 enzymes targeted by the oligomers according to SEQ ID NO: 16, 18-20, 23-25, 35-36, and 46-47 in the claimed methods.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-9, 13-15, and 25-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of issued US Patent No. 6,686,338 and claims 1-15 of US Patent No. 6,673,778. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and those of the issued US Patents are both drawn to a method of inhibiting the metabolism of a drug administered to a subject comprising co-administering with said drug a morpholino antisense oligomer to said subject.

The claims of the issued US Patents are drawn to methods comprising the administration of specific species of antisense oligonucleotides targeting a particular cytochrome P450 variant. However, the instant claims are drawn to a broad genus of antisense compounds used in the same methods which comprise administration of a morpholino antisense oligomer targeting cytochrome P450 in combination with a drug. Therefore since the scope of the claims of the instant application encompass the methods comprising the administration of the specific species of antisense oligomers recited in the issued US patents, the claims of the issued US Patents are considered to anticipate the claims of the instant application.

Notice of References Cited (PTO-892)

7. With the exception of US Patent Nos. 6,686,338 and 6,673,778, all of the references cited above were previously forwarded to Applicants during the prosecution of parent application 09/574,570.

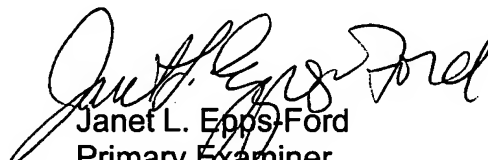
Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.


Janet L. Epps-Ford
Primary Examiner
Art Unit 1633

JLE